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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/626,229	07/24/2003	Jean-Claude Reubi	717816.23	4549

27128 7590 04/11/2006

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EXAMINER	
PHAM, AUDREY S	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/626,229	REUBI, JEAN-CLAUDE	
	Examiner	Art Unit	
	Audrey S. Pham	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-9,12-14,23-25 and 27-36* is/are pending in the application.

4a) Of the above claim(s) *1-3,6-9,23-25,27,28 and 32-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-14 and 27-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *APPENDIX 1*.

DETAILED ACTION

Examiner's Response Election/Restriction

The Election filed on January 13, 2006, in responses to the Office Action Requirement for Restriction dated October 07, 2005 and in response to the Notice of NonCompliant dated December 19, 2005 are acknowledged and has been entered. Applicant elected, with traversed, Group VII, Claims 12-14, 25, 27-31, drawn to a labeled peptide and to a pharmaceutical composition for controlling CCK-receptor expressing tumor comprising a peptide formula wherein the peptide is attached to an isotope or atom by a chelating group. Applicant further elects SEQ ID NO: 21 for examination.

Applicant's traversal is on the ground that SEQ ID NO: 13, 14, 19, 20, 21, 22, and 23 represent species of SEQ ID NO: 27 recited in the generic claim 12, and therefore should be entitled to the consideration of the species represented by SEQ ID NO: 13-14, 19-23.

Upon review and reconsideration, it is found that Applicant is indeed correct and that Claim 12, in fact, links the claimed sequences. Thus, in response to Applicant's traversal and with Applicant's approval, restriction of the elected group VII is required under 35 USC §121.

Claim 12, drawn to a pharmaceutical composition for a human subject comprising a general formula SEQ ID NO: 27, links inventions 1-7 as set forth below. The restriction requirement among the linked inventions is subject to the nonallowance of the linking claim. Upon the allowance of the linking claim, the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim will be rejoined and fully examined for patentability in accordance with 37 CFR 1.104.

Applicant was advised, in the telephone interview of March 14, 2006, that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting

rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

1. Claims 13, 27-29, 31 drawn to the pharmaceutical composition, a labeled peptide and the method of making said composition thereof, wherein the active substance is a derivatized peptide that is selected from SEQ ID NO: 19, classified in class 514, subclass 2.

2. Claims 13-14, 27-31 drawn to the pharmaceutical composition, a labeled peptide and the method of making said composition thereof, wherein the active substance is a derivatized peptide that is selected from SEQ ID NO: 20, classified in class 514, subclass 2.

3. Claims 13-14, 27-31 drawn to the pharmaceutical composition, a labeled peptide and the method of making said composition thereof, wherein the active substance is a derivatized peptide that is selected from SEQ ID NO: 21, classified in class 514, subclass 2.

4. Claims 13, 27-29, 31 drawn to the pharmaceutical composition, a labeled peptide and the method of making said composition thereof, wherein the active substance is a derivatized peptide that is selected from SEQ ID NO: 22, classified in class 514, subclass 2.

5. Claims 13, 27-29, 31 drawn to the pharmaceutical composition, a labeled peptide and the method of making said composition thereof, wherein the active substance is a derivatized peptide that is selected from SEQ ID NO: 23, classified in class 514, subclass 2.

6. Claims 25, 31, drawn to the pharmaceutical composition and the method of making said composition thereof, wherein the peptide is SEQ ID NO: 13. classified in class 514, subclass 2.

7. Claims 25, 31, drawn to the pharmaceutical composition and the method of making said composition thereof, wherein the peptide is SEQ ID NO: 14, classified in class 514, subclass 2.

The inventions of groups 1-7 encompass multiply distinct and independent products that encompass different functional as well as structural formulas. Each group encompasses different peptides, each of which has different amino acid makeup and thereof each is patentably distinct. Because each group is distinct, searching the invention of one group would not be co-extensive with the other groups. Also, the patentability of one group would not be used to determine the patentability of the other groups. Thus, searching all the groups would impose a serious burden. Applicant is reminded that the reply to this requirement to be completed must include an election of the invention to be examined even though the requirement be traversed (See 37 CFR 1.143).

In a telephone interview on March 14, 2006, with Mr. Charles Romano and Mr. Kevin Kercher, the examiner informed Applicant that the elected claims were properly restrictable under linking claim practice and suggested perfecting the restriction of Group VII (prior Office Action) under linking claim practice. Mr. Romano and Mr. Kercher approved the re-restriction of the elected Group VII and again elected SEQ ID NO: 21 for examination. Thus, the claims currently under prosecution are Claims 12-14, 27-31 as they are drawn only to SEQ ID NO: 21. Therefore, Claim 25 is withdrawn as being drawn to non-election invention. For the election of species, Applicant elected the radioactive metal isotope ^{111}In, paramagnetic metal atom Gd, radioactive halogen isotope ^{125}I, and the chelating group DOTA. Claims 12-14, 27-31 are under consideration.

Affirmation of this telephone election in writing is required in response to this action.

Priority

This application is claiming the benefit of the prior-filed Nonprovisional Application Serial No 09/125823 under 35 U.S.C. 120, 121, or 365(c). Upon review of the petition, filed on May 06, 2003 and granted on September 9, 2003, to revive the abandoned application solely for the purpose of establishing continuity with the instant application, the benefit of priority under SN 09/12582 is accepted.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on August 26, 2004 and May 07, 2004 and March 25 2004 (in part) are considered by the examiner. However, the references Reubi *et al.* (Cancer Research, Vol 57, Issue 7, pages 1377-1386) and Mailleux *et al.* (Neuroscience Letters, 1990, Vol 117, Issue 3, pp 243-247) listed on the IDS dated March 25, 2004 were not considered because the documents were not submitted.

Specification

1. The abstract of the disclosure, amended on April 20, 2004, is objected to because the abstract contains legal phraseologies such as "comprising," "said being," "thereof," etc. Corrections are required. See MPEP § 608.01(b). Applicant is reminded of the proper language and format for an abstract of the disclosure. The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details. The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

2. The Brief Description of the Drawing is objected to because the section describing figures 1-4 describes displacement curves of compound 15 and compounds 13-14. However, Figures 1-4 of the Drawings shows displacement curves for different compounds. For example, the Brief Description describes Figures 1A-C as showing displacement curves of $^{[125]}$I-CCK-10 analog (compound 15) binding to tissue sections from three different tumors. However, Figures 1A-C of the Drawing show binding displacements of Compound 16, Compound 17 and SS-14. Also, the term "SS – 14" is not described in the specification. Appropriate corrections are required. Applicant is reminded that no new matter may be introduced.

Claim Objections

1. Claim 12 is objected to because the claim contains the character **"(I)"** in the general formula H-$(Xaa)_n$-$(Xbb)_m$-Tyr-Xcc-Gly-Trp-Xdd-Asp-Phe-R_2**(I)** that is not defined. Appropriate correction is required.

2. Claim 14 is objected to under 37 CFR 1.75(c) as being of improper dependent form for failing to further limit the subject matter of Claim 13. Claim 13 is drawn to the pharmaceutical composition of Claim 12 wherein the active substance is a derivatized peptide that is SEQ ID NO: 21, wherein said peptide is labeled with a metal isotope or atom attached to the peptide by means of a chelating group chelating said isotope or atom, wherein said chelating group is bound by an amide bond or through a spacing group to the peptide molecule. Claim 14 is drawn to the composition of Claim 13 wherein said derivatized peptide is SEQ ID NO: 21.

3. Claims 29-30 are objected to under 37 CFR 1.75(c), as being duplicates of each other. Specifically, both Claims 29 and 30 are drawn to a labeled peptide of Claim 12 wherein said peptide comprises DTPA and is SEQ ID NO: 21. Appropriate correction is required.

Claim Rejections – 35 USC §112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27-30 recite the limitation "[t]he labeled peptide of Claim 12", however Claim 12 is drawn to a pharmaceutical composition comprising a pharmaceutically acceptable carrier, at least one pharmaceutically acceptable adjuvant, and a peptide. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 12-14, 27-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the ENABLEMENT requirement. The specification, while enabling for a composition comprising SEQ ID NO: 21 for *in vitro* detection of CCK-B receptor, does not reasonably provide enablement for a pharmaceutical composition for combating or controlling tumors as claimed in the instant application or for *in vivo* imaging, as inferred by the claims and contemplated by the specification. The claims contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention.

According to *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1998), the claimed invention should be enabled so that any person skilled in the art can make and use the invention without undue experimentation. See also *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.") See also MPEP § 2164.01(a) and § 2164.04. Factors to consider in determining whether undue experimentation

is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). The factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are drawn to a pharmaceutical composition comprising, in addition to a pharmaceutical acceptable carrier material and, if desired, at least one pharmaceutically acceptable adjuvant, as the active substance, in a quantity sufficient for external imaging, or detection by gamma detecting probe or for combating or controlling tumors, a peptide of the general formula H-$(Xaa)_n$-$(Xbb)_m$-Tyr-Xcc-Gly-Trp-Xdd-Asp-Phe-R_2 (SEQ ID NO: 27) or an acid thereof, formed between a free NH_2 group of an amino acid moiety and R_1COOH; or a lactam thereof, formed between a free NH_2 group of an amino acid moiety and a free CO_2H group of another amino acid moiety or a conjugate thereof with avidin or biotin, wherein one or more of the amino acids of said peptide can be in the D-configuration and wherein said peptide may comprise pseudo peptide bonds said peptide being labeled with (a) a radioactive metal isotope ^{111}In or (b) with a paramagnetic metal atom that is GD or (c) with a radioactive halogen isotope that is ^{125}I (Claims 12); wherein said active substance is a derivatized peptide that is SEQ ID NO: 21 (Claims 13-14, 29-30); wherein said metal isotope or said metal atom is attached to the peptide by means of a chelating group chelating said metal isotope or said metal atom wherein said chelating group is bound by an amide bond or through a spacing group to the peptide molecule (Claim 27); wherein said chelating group is DOTA (Claim 28).

The specification proposes to provide a method of detecting and localizing malignant tumors that are difficult to characterize, such as Small Cell Lung Carcinoma and Medullary Thyroid Carcinoma (page 1, lines 24-29) by administering a peptide of SEQ ID NO: 27 in a quantity sufficient for external imaging (page 2, lines 20+). The specification further teaches that such objectives can be achieved by administering to said being a composition comprising, in a quantity sufficient for detection by gamma detecting probe, a peptide derived from a compound of the general formula, as defined above or an acid amide thereof (page 5, lines 7-11). The specification teaches that certain carcinomas such as Small Cell Lung Carcinoma and Medullary Thyroid Carcinoma, breast carcinoma, stromal ovarian carcinoma, and muscle

carcinoma, in addition to CCK normally expressing in the gastrointestinal tract, express a detectable amount of CCK receptors (page 3, lines 23-29). The specification further discloses that it surprisingly found that CCK analogs will preferentially recognize CCK-A or CCK-B receptor-expressing tumors depending on the sulfation state of CCK and analogs (page 3, lines 29-35). The unsulfated CCK and analogs will specifically recognize CCK-B receptors, which are found in breast carcinoma, ovarian carcinoma, and sarcoma, but not found in non-small cell lung carcinoma and non-medullary thyroid cancers (bridging paragraph of pages 3-4). The normal sulfated CCK and analogs will recognize both CCK-A and CCK-B receptors wherein CCK-A is found in non-small cell lung carcinoma and non-medullary thyroid cancers, but rarely found on breast cancer, ovarian cancer or sarcoma (page 3, lines 31-35, page 4, lines 1-6). Accordingly, the CCK-B receptors can be specifically labeled with adequate CCK analogs (page 4, lines 5-6) in which suitable examples includes peptides of SEQ ID NO: 1-11 (page 6, lines 13-37) and SEQ ID NO: 13-14 (page 11, lines 16-17). The specification further discloses that the peptides can be labeled with a metal atom attached to the peptides by means of a chelating group chelating said atom, which chelating group is bound by an amide bond or through a spacing group of the peptide molecule (page 7, lines 8-19). The specification discloses a general method of making SEQ ID NO: 12 (compound 12) by Chiron-Multipin Synthesis Technology (page 15, lines 15-25), a method of making CCK analogs and DTPA containing CCK analogs (page 15, line 27+), and a method of making labeled compounds 25 and 26 (SEQ ID NO: 25-26) (page 17, lines 20+). The specification teaches labeling ^{115}In labeled compounds 25 and 26 (page 17, line 20+). Given the data in Figure 2, it is clear that SEQ ID NO: 21 is an unsulfated analog since it binds to CCK-B receptors but not to CCK-A receptors.

One of ordinary skill in the art cannot extrapolate the teachings of the specification to the scope of the claimed subject matter because the claims of the instant invention are drawn to a subject matter (a pharmaceutical composition) that is distinctly different from what is disclosed (a labeled peptide). Webster's Third New International® Dictionary, Unabridged, Copyright © 1993 defines "pharmaceutical" as a medicinal drug (APPENDIX 1) and inherent in the medicinal drug is the *in vivo* use thereof for treatment. In addition, the claims recite the intended uses of the pharmaceutical composition for combating or controlling *all types* of tumors. It cannot be predicted from the information in the disclosure that the labeled peptide can be extrapolated to a pharmaceutical composition for combating or controlling all types of tumors. The specification fails to provide any *in vitro* or *in vivo* teachings of the efficacy of tumor

inhibition by the novel, newly discovered labeled peptides. As such, one skilled in the art would not know how to use the pharmaceutical composition to treat cancer based only on the teachings in the specification of *in vitro* displacement studies showing that some labeled peptides bind to cancer tissues.

Those of skill in the art recognize that *in vitro* assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in-vitro* assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (1983, Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences In Vitro). Further, Dermer (1994, Bio/Technology, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that *in vitro* assays cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

As drawn to the treatment of combating or controlling tumors, one cannot extrapolate the teaching of the specification to the enablement of the claims because it is well known in the art that anticancer drug discovery for cancer therapy is highly unpredictable and Applicant has claimed, but not taught, a pharmaceutical composition comprising labeled peptides as an anti-cancer agents. Gura (1997, *Science*, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile. Gura also teaches that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). As drawn to the unpredictability of the cancer therapy arts, the refractory nature of cancer to drugs is well known in the art. Jain (1994, *Sci. Am.*, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (1993, *Crit. Rev. in Oncology/Hematology*, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2).

Further, a labeled peptide must accomplish several tasks to be effective toward tumor tissues *in vivo*. It must be delivered into the circulation that supplies the tumor and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. In addition, the target cell must not have an alternate means of survival despite action at the proper site for the agent. *In vitro* assays cannot duplicate the complex conditions of *in vivo* therapy. In the assays, the agent is in contact with cells during the entire exposure period. This is not the case *in vivo*, where exposure at the target site may be delayed or inadequate. In addition, variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The claimed pharmaceutical composition may be inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation,

immunological activation or due to an inherently short half life of the labeled peptides and *in vitro* tests, even if were performed, would not sufficiently duplicate the conditions which occur *in vivo*. In addition, the claimed pharmaceutical composition may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by cells and tissues where the labeled peptide has no effect, circulation into the target area may be insufficient to carry the claimed pharmaceutical composition and a large enough local concentration may not be established. For the above reasons, it appears that undue experimentation would be required to practice the claimed inventions with a reasonable expectation of success. Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the pharmaceutical composition comprising an untested labeled peptide of a general formula, from which derivations and species thereof may be used, could target and function as claimed, based on binding studies showing curve displacements.

As drawn to using external imaging, the specification fails to provide an adequate teaching on the issue of CCK receptor sequestration. There is no information as to the amount of CCK receptors that are present and that are required to be present on the cell surface for a labeled peptide to bind for adequate detection by external imaging. One cannot predict that the CCK-A and CCK-B receptors are exposed in sufficient quantities on the surface of malignant cells in human *in vivo*, and that the malignant cells are accessible by the labeled peptides for external imaging. Although drawn to immunotherapy, the teachings of White *et al.* are relevant to the instant rejection. White et al. (2001, Ann. Rev. Med. 52:125-145) teach that for a successful immunotherapy, besides specificity of the antigen, other properties of the antigen should be considered such as the following: (1) that the antigen should be present on all or near all of the malignant cells to allow effective targeting and to prevent a subpopulation of antigen-negative cells from proliferating; and (2) whether the antigens shed, modulate or internalize influence the effectiveness of the administered immunotherapy (i.e. the antibody) (p. 126, second paragraph). Additionally, antigen internalization or downregulation can cause repeat dosing to be unsuccessful due to the disappearance of the antibody target (p. 126, paragraph before last). In the instant application, variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The peptides may be inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein. In addition, the

peptides may not otherwise reach the target because they may not penetrate tissues or cells where activities are to be exerted. The peptides may be absorbed by fluids, cells and tissues where they have no effect, and circulation into the target area may be insufficient to carry the peptides so that a large enough local concentration of the peptides may not be established. Thus, the teaching of White is applicable to the instant case because a pharmaceutical composition must be able to find the target expressed on the surface of malignant cells. In the instant case, the specification fails to provide adequate control and fails to provide objective evidence that cancer cells display the CCK receptors in sufficient quantity on the surface for the labeled peptides to recognize and target said cells and to effectively provide sufficient signal for external imaging. Given the above, it would require undue experiment to practice the claimed invention.

Disclosure of working examples is given added weight in cases involving an unpredictable and undeveloped art such as the treatment of cancer with labeled peptides. The specification provides no objective evidence or working examples to lend one of ordinary skill in the art a reasonable expectation of success of treating *all* cancers. In view of the teachings above, and the lack of guidance and/or examples in the specification, it would not be predictable for one of ordinary skill in the art to use the pharmaceutical composition to combat or control tumors. With the claims broadly drawn, the guidance limited, and the art being unpredictable, it would require undue experimentation for one of ordinary skill in the art to successfully practice the invention as claimed. Therefore, the claims are enabled for a labeled peptide comprising a peptide of SEQ ID NO: 21 for in vitro detection, but not for a pharmaceutical composition comprising a peptide SEQ ID NO: 21 for combating or controlling tumors or for external imaging.

2. Claims 12-13, 27-28, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the ENABLEMENT requirement. The specification, while enabling for *in vitro* detection of CCK-B receptor by external imaging or for gamma detection by a detecting probe for a composition comprising SEQ ID NO: 21, does not reasonably provide enablement for a composition comprising the general formula of SEQ ID NO: 27 for external imaging or for combating or controlling tumors. The claims contain subject matter that was not described in

the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention.

The claims are drawn to a pharmaceutical composition comprising SEQ ID NO: 27 as set forth above.

The specification teaches as set forth above.

One cannot extrapolate the teaching of the specification to the scope of the claims because specification fails to provide objective evidence or working examples to show that any of the species that includes modifications and derivations of SEQ ID NO: 27 can be used to successfully treat tumors. Those of skill in the art recognize that protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Burgess *et al.* (J. Cell Biol. 111:2129-2138, 1990) shows that a conservative replacement of a single "lysine" residue at position 118 of acidic fibroblast growth factor by "glutamic acid" led to a substantial loss of heparin binding, receptor binding and biological activity of the protein. Similarly, Lazar *et al.* (Mol. Cell Biol. 8:1247-1252, 1998) teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 alone with alanine or asparagines did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. Wen *et al.* (Proc. Natl. Acad. Sci. U.S.A. 98: 4622-4627, 2001) demonstrate that a mutation in PTEN (G129D), a phosphatase with specificity for 3-phosphorylated inositol phospholipids, impaired the lipid phosphatase activity and its role in angiogenesis. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristics of a protein. Additionally, Bowie et al (*Science*, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to

the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). However, Applicant provides no teaching to enable one of skilled in the art to predictably identify or differentiate between those polypeptides that will function as claimed and those that will not not. Therefore, absent the evidence that the broadly claimed general formula SEQ ID NO: 27 can be used as a pharmaceutical composition for external imaging or for combating or controlling tumors, one of skill in the art would not be able to predictably use the broadly claimed species of SEQ D NO: 27 as a pharmaceutical composition to control or combat tumors without undue experimentation.

It appears that Applicant is suggesting random experimentation or screening with the labeled peptides linked to DPTA and containing non-natural amino acids, both known and unknown, specific for any cells exhibiting CCK-A or -B receptors, with any avidity, in order to discover ones that will function as claimed. Applicant is reminded that screening assays do not enable the claimed invention because the court found in *Rochester v. Searle* (358 F.3d 916, fed Cir., 2004) that screening assays are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed invention.

In view of the teachings above, and the lack of guidance and/or examples in the specification, the breadth of the claims, the limited guidance, and the art being unpredictable, it would require undue experimentation for one of ordinary skill in the art to successfully practice the invention as claimed.

3. Claims 12-14, 27-28, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the ENABLEMENT requirement. The specification, while enabling for a composition comprising SEQ ID NO: 21 for *in vitro* detection of CCK-B receptor in breast carcinoma, ovarian carcinoma, and sarcoma, does not reasonably provide enablement for a composition comprising SEQ ID NO: 21 for *in vitro* detection of CCK-B receptors in non-small cell lung carcinoma and non-medullary thyroid cancers or other types of tumors, as inferred by the claims and contemplated by the specification. The claims contain subject matter that was

not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention.

The claims are drawn to a pharmaceutical composition for external imaging or detection by gamma detecting probe as set forth above.

The specification teaches as set forth above.

is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

One skilled in the art cannot extrapolate the teaching of the specification to the scope of the claims because it cannot be predicted from the disclosure that all types of tumors can benefit from the use of the composition as inferred by the claims and as contemplated by the specification. The specification teaches that SEQ ID NO: 21 binds only to the CCK-B receptor (Figure 2A), but not to the CCK-A receptor (Figure 2B). The specification also teaches that the CCK-B receptors are found in breast carcinoma, ovarian carcinoma, and sarcoma, whereas CCK-A receptors are found in non-small cell lung carcinoma and non-medullary thyroid cancer. Thus, one skilled in the art could not use SEQ ID NO: 21 to detect binding in non-small cell lung carcinoma and non-medullary thyroid cancer. Also, the specification does not clearly indicate whether other types of tumors specifically express CCK-A or CCK-B or both. Absent evidence of the CCK-B's expression including the correlation to other diseased states, one of skill in the art would not be able to predictably use SEQ ID NO: 21 in a diagnostic or treatment setting for other types of tumors without undue experimentation. Reasonable correlation must exist between the scope of the claims and the scope of the enablement set forth. In view of the quantity of experimentation necessary the limited working examples, the nature of the invention,

the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 12, 27-28, 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gubler et al (1984, PNAS, 81:4307-4310), in view of Slaninova et al (1995, Peptides 16(2):221-224), in further view of Dean *et al.* (1991, US Patent No 5,053,503).

The claims are drawn to a pharmaceutical composition comprising, in addition to a pharmaceutical acceptable carrier material and, if desired, at least one pharmaceutically acceptable adjuvant, as the active substance, in a quantity sufficient for external imaging, or detection by gamma detecting probe or for combating or controlling tumours, a peptide of the general formula H-$(Xaa)_n$-$(Xbb)_m$-Tyr-Xcc-Gly-Trp-Xdd-Asp-Phe-R_2 (SEQ ID NO: 27) or an acid

thereof, formed between a free NH_2 group of an amino acid moiety and R_1COOH; or a lactam thereof, formed between a free NH_2 group of an amino acid moiety and a free CO_2H group of another amino acid moiety or a conjugate thereof with avidin or biotin, wherein one or more of the amino acids of said peptide can be in the D-configuration and wherein said peptide may comprise pseudo peptide bonds said peptide being labeled with (a) a radioactive metal isotope ^{111}In **or** (b) with a paramagnetic metal atom that is GD **or** (c) with a radioactive halogen isotope that is ^{125}I (Claim 12); wherein said metal isotope or said metal atom is attached to the peptide by means of a chelating group chelating said metal isotope or said metal atom wherein said chelating group is bound by an amide bond or through a spacing group to the peptide molecule (Claims 13); wherein said chelating group is DOTA (Claim 28). Claim 31 is drawn to a method of preparing a labeled peptide of the general formula.

Gubler *et al.* teach a cholecystokinin octapeptide CCK8 peptide and its synthesis thereof (p 4307, col 1, para 2) comprising the sequence H-Asp-Tyr-Met-Gly-Trp-Met-Asp-Phe-NH_2 (p 4307, col 2 line 1) which is a species of the general formula H-$(Xaa)_n$-$(Xbb)_m$-Tyr-Xcc-Gly-Trp-Xdd-Asp-Phe-R_2. Gubler *et al.* further teach the amino acid sequence of CCK8 with the COOH-terminally amidated phenylalanine (page 4307, column 2, Figure 1 caption).

Gubler *et al.* do not teach said peptide being labeled with (a) a radioactive metal isotope ^{111}In **or** (b) with a paramagnetic metal atom that is GD **or** (c) with a radioactive halogen isotope that is ^{125}I, wherein said metal isotope or said metal atom is attached to the peptide by means of a chelating group chelating said metal isotope or said metal atom wherein said chelating group is bound by an amide bond or through a spacing group to the peptide molecule, wherein said chelating group is DTPA or DOTA.

Slaninova *et al.* teach a CCK8 analogue comprising [3H]Asp-Tyr-N-MeNle-Gly-Trp-N-MeNle-Asp-Phe-NH2 radiolabeled with ^{125}I radioactive halogen isotope (page 223, column 1 line 1).

Dean *et al.* specifically teach a bifunctional chelating agent DOTA (column 2 lines 34-42) for joining an antibody or antibody fragment with a radiometal ^{111}In to form radiodiagnostic or radiotherapeutic agents (column 6 lines 23-27). Dean *et al.* further teach that the bifunctional chelating agent is selected such that it is capable of binding radiometals by chelation as well as forming a linkage to the protein (column 1, lines 35-38). Dean *et al.* teach

the advantages of DOTA chelators such as (1) providing high stability thereby reducing the incidence of background during imaging procedures or damage to non-targeted tissues in radioimmunotherapy (2) having a cleavable group in the organic linking radical portion of the molecule which results in decreased accumulation of radiolabeled protein in tissues other than those which comprise specific binding sites of the protein (column 2 lines 54-66). Dean *et al.* teach that DTPA has also been used to chelate ^{111}In to a protein (column 1, lines 38-41). Finally, Dean *et al.* teach a method for preparing the labeled peptide using the chelating agent to join the peptide and the radionuclide (col 5, lines 29-31). Specifically, the protein is joined to the chelating agent via an organic linking radical (i.e., a spacing group) selected from substituted alkyl, aryl, alkoxy, hydroxyl, or carboxyl groups (col 3-4, bridging paragraph; see also Table 1, col 5-8). The peptide-chelating agent group is linked to the ^{111}I metal atom in the form of a salt of the radiometal in a suitably buffered solution (col 6, lines 23-35).

It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made, to attach the peptide of Gubler to a radioactive ligand via DOTA chelating agent because such labeled CCK peptides have been used in radioimaging to study binding inhibitions (Slaninova, abstract) and thus are useful in research, for developing diagnostic *in vivo* or screening methods. One of ordinary skilled in the art would have also been motivated to attach an ^{111}I through a DTPA or DOTA chelating agent to the peptides in view of the fact that Dean *et al.* taught the agent is capable of binding radiometals as well as forming a linkage to the protein (column 1, lines 36-38) and such radiolabeling is used to trace activities of peptides. Finally, one would have a reasonable expectation of success in using the labeled peptides attached to ^{111}I via a chelating agent for radioimaging because the combination of the prior art references teach that such combinations of radiolabeled peptides can be used for detecting binding in tissues.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 12-14, 27-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gubler et al (1984, PNAS, 81:4307-4310), in view of Slaninova et al (1995, Peptides 16(2):221-224), in further view of Dean *et al.* (1991, US Patent No 5,053,503) and in further view of Black *et al.* (1995, US Patent No. 5,416,013)

The claims are drawn to a pharmaceutical composition comprising, in addition to a pharmaceutical acceptable carrier material and, if desired, at least one pharmaceutically acceptable adjuvant, as the active substance, in a quantity sufficient for external imaging, or detection by gamma detecting probe or for combating or controlling tumours, a peptide of the general formula H-$(Xaa)_n$-$(Xbb)_m$-Tyr-Xcc-Gly-Trp-Xdd-Asp-Phe-R_2 (SEQ ID NO: 27) or an acid thereof, formed between a free NH_2 group of an amino acid moiety and R_1COOH; or a lactam thereof, formed between a free NH_2 group of an amino acid moiety and a free CO_2H group of another amino acid moiety or a conjugate thereof with avidin or biotin, wherein one or more of the amino acids of said peptide can be in the D-configuration and wherein said peptide may comprise pseudo peptide bonds said peptide being labeled with (a) a radioactive metal isotope ^{111}In **or** (b) with a paramagnetic metal atom that is GD **or** (c) with a radioactive halogen isotope that is ^{125}I (Claim 12); wherein said active substance is a derivatized peptide that is DTPA-DAsp-Tyr-Nle-Gly-Trp-Nle-Asp-Phe-NH_2 (SEQ ID NO: 21) (Claims 14, 29-30); wherein said

metal isotope or said metal atom is attached to the peptide by means of a chelating group chelating said metal isotope or said metal atom wherein said chelating group is bound by an amide bond or through a spacing group to the peptide molecule (Claims 13); wherein said chelating group is DOTA (Claim 28). Claim 31 is drawn to a method of preparing a labeled peptide of the general formula.

Gubler *et al.* teach as set forth above.

Gubler *et al.* do not teach one or more amino acid of said peptide in the D-configuration and wherein said peptide may comprise pseudo peptide bonds said peptide being labeled with (a) a radioactive metal isotope ^{111}In **or** (b) with a paramagnetic metal atom that is GD **or** (c) with a radioactive halogen isotope that is ^{125}I, wherein said metal isotope or said metal atom is attached to the peptide by means of a chelating group chelating said metal isotope or said metal atom wherein said chelating group is bound by an amide bond or through a spacing group to the peptide molecule, wherein said chelating group is DTPA.

Slaninova *et al.* teach a CCK8 analogue comprising [3H]Asp-Tyr-N-MeNle-Gly-Trp-N-MeNle-Asp-Phe-NH2 radiolabeled with ^{125}I radioactive halogen isotope (page 223, column 1 line 1). Slaninova *et al.* further teach the advantages of replacing of both methionines at positions 3 and 6 with stable amino acids to yield good radioligand and high affinity for CCK receptors (page 221, column 1 paragraph 1).

Dean *et al.* teach that DTPA has also been used to chelate ^{111}In to a protein (column 1, lines 38-41).

Black *et al.* teach that changing the L-aspartate residue to D-aspartate profoundly increase ability of proteolytic enzyme Interleukin 1β to cleave the peptide substrate (column 3 line 52-55, column 25, lines 30-33) which Dean *et al.* taught is needed to prevent peptide accumulation in the system after detection assays (see above).

It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made, to make the labeled peptides of SEQ ID NO: 21 to the specificities taught by the prior art. First, it would have been obvious and one of ordinary skill in the art would have been motivated to make the derivative peptides represented by SEQ ID NO: 21 in view of the fact that Slaninova teach the advantages of replacing of both methionines (at positions 3 and 6)

with stable amino acids such as Norleucines to yield good radioligand and high affinity for CCK receptors (page 221, column 1 paragraph 1). Second, it would have been obvious and one of ordinary skilled in the art would have been motivated to attach the peptides to radioligands because such labeled CCK peptides have been used in radioimaging to study binding inhibitions (Slaninova, abstract) and thus are useful in research, for developing diagnostic *in vivo* or screening methods. Third, it would have been obvious and one of ordinary skilled in the art would have been motivated to attach an ^{111}I through a chelating agent to the peptides in view of the fact that chelating agent is routinely used link metals to peptides or proteins and that DTPA is a common chelating agent. In addition, Black et al have demonstrated the successful modification of L-aspartate to D-aspartate at position 1 of a peptide to increase the ease of cleaving the peptide substrate and Dean *et al.* taught having a cleavable group will decease the likelihood of radiolabeled peptide accumulating in tissues. Finally, one would have a reasonable expectation of success in using the labeled peptides attached to ^{111}I via a DTPA chelating agent for radioimaging because the combination of the prior art references teach that such combinations of radiolabeled peptides can be used for detecting binding in tissues.

Conclusion

No claim is allowed.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Audrey S. Pham whose telephone number is (571) 272-3323. The examiner can normally be reached during the hours of 8:30 AM - 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached during business hours at the telephone number: (571) 272-0787. The fax number for the organization, where this application or proceeding is assigned, is (571) 273-8300.

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PRIMARY EXAMINER

Reference Shelf

APPENDIX 1

Webster's Dictionary : Full Text

CLOSE WINDOW | HELP | ABOUT | MODIFY SEARCH

<<Previous headword | Next headword>>
Back to results

[2]pharmaceutical *n* -S

: a pharmaceutical preparation : medicinal drug